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A New Approach to Modelling the Formation of Necrotic Regions in Tumours

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Abstract—We present a mathematical model of the growth of tumours. The cells in the tumour are taken to proliferate and die at rates determined by the concentration of oxygen which diffuses into the tumour across its surface. Tumour cells are assumed to be composed primarily of water while the extracellular water is taken to move through the tumour as a porous media flow between the cells. Exchange of water between the two is governed by cell proliferation. We model the mass of cells as an inviscid fluid with the pressure in the fluid, keeping the cells loosely packed together. Cells move in response to pressure in both fluids until the extracellular water pressure exceeds the cell pressure, resulting in the rupture of the tumour cells as they are ripped from one another. The resulting model is one of porous media flow with distributed sources and sinks determined by the oxygen concentration. The boundary conditions change type depending on whether the tumour surface is retreating or advancing. Retreating interfaces leave ruptured cells creating necrotic regions. An example of the model behaviour in one dimension is presented.

Keywords—Tumour, Pressure, Cell movement, Porous media, Hele-Shaw, Moving boundary, Necrosis.

INTRODUCTION

There has been considerable interest in the modelling of tumours since Greenspan [1] with particular interest in their dynamic behaviour [2–5]. One of the main characteristics of many tumours is their partitioning into a number of adjacent regions. The outermost region contains cells that are growing rapidly. Deeper into the tumour the next region is characterised by more quiescent cells, with the innermost necrotic region consisting of extracellular water, cell debris, and cell wastes. Most of the models to date have assumed this necrotic region exists due to rapid cell death, usually in response to low oxygen levels or other diffusing nutrients. However, there has been little specific modelling on how such a necrotic region might appear, its existence being assumed to occur at some critical oxygen concentration (e.g., [3]), and hence no direct attempts have been made to include the forces determining the necrotic region dynamics. There are a number of recent papers looking more carefully at the forces acting in tumours due to visco-elastic effects [2,6,7], but these have yet to be used to predict necrotic behaviour. In this paper, we

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present a simple model which avoids many of the problems associated with nonlinear-elasticity theory and attempts to give an explanation of the cell dynamics in a tumour body. We investigate a specific geometry in order to illustrate that the observed behaviour can be predicted by this model. This work is currently being extended to describe the growth pattern of multicell spheroids, *in vitro* and *in vivo* cancers.

MATHEMATICAL MODEL

We consider a mathematical model of tumour growth, incorporating the development of regions of necrosis, wherein the tumour is regarded as occupying a region which changes in shape as time progresses. Within this region, consisting of tumour cells and extracellular water, we consider three main physical processes:

(i) the diffusion of oxygen,
(ii) the conservation of water, and
(iii) the forces acting on the extracellular water and the cells.

A schematic of the flow processes involved is shown in Figure 1.

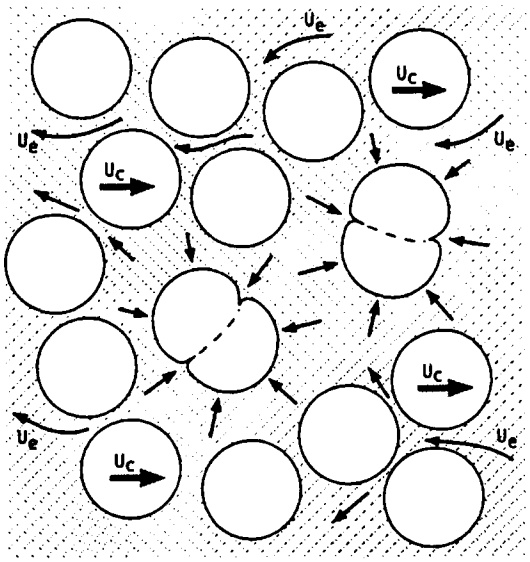

Figure 1. Schematic of the flow of extracellular water $\mathbf{U}_e$ and the flow of cells and extracellular matrix $\mathbf{U}_c$. Cell division and growth, involving the uptake of extracellular water, is also illustrated.

The diffusion and consumption of oxygen is an essential component of this model as we assume it is the oxygen concentration that determines the rate at which tumour cells proliferate or die. Assuming that the cells within the tumour body are essentially composed of water, then water is conserved as tumour cells die (converting cells into water) or proliferate (converting water into cells). We wish to show that the interaction of forces acting on the extracellular water and the tumour cells may be used to determine the rate of tumour growth and the development of necrotic regions within a tumour body.

Considering the diffusion of oxygen to be very rapid, with diffusion coefficient D, the oxygen concentration $C(\mathbf{x}, t)$ throughout the tumour satisfies the quasi-static equation

$$D\nabla^2 C = aC, \tag{1}$$

where we assume, for the purposes of illustration, that the oxygen uptake rate by live cells is proportional to the local oxygen concentration with a being the rate constant.

We consider the tumour cells to be made entirely of incompressible water and that the rate at which extracellular water is converted to cells is given by $S(C)$ (because the definition of the

velocities $S(C)$ is the volume of cells produced in a unit time in a unit volume of the tumor). A simple model of this conversion rate we will employ here is $S(C) = dC - e$, where d and e are constants. Note that $S(C) < 0$ corresponds to cells dying and turning into extracellular water. Taking the cells to move at a superficial velocity of $\mathbf{U}_c$, with an actual velocity of $\mathbf{U}_c/(1-\phi)$, where ϕ is the volume fraction of extracellular water for a given tumour volume, we have

$$\nabla \cdot \mathbf{U}_c = S(C).$$

Similarly, the extracellular water with superficial velocity $\mathbf{U}_e$ satisfies

$$\nabla \cdot \mathbf{U}_e = -S(C).$$

Extracellular water flows between the cells of the tumour body, with the cell mass acting like a porous media, and hence the force balance on the water is given by

$$\mathbf{U}_e - \frac{\phi}{1-\phi}\mathbf{U}_c = -k\nabla P_e, \tag{2}$$

where P_e is the extracellular water pressure and k is the constant permeability. Finally, considering the cell motion, we take the simplest possible model where the cells act inviscidly, and so the overall force balance requires that

$$\phi \nabla P_e = -(1-\phi)\nabla P_c, \tag{3}$$

where P_c is the pressure acting between cells. This intercellular force can act between cells, independently of the extracellular water pressure, via the extracellular matrix surrounding the cells. Note that this cell pressure may be different from the internal pressure of the cells which can be modified, for example, by osmotic pressures across cell membranes.

For the purposes of the modelling here, it is sufficient to consider those situations where the solution to the above system satisfies

$$\mathbf{U}_e = -\mathbf{U}_c \quad \text{and} \quad P_e - p_o = -\frac{1-\phi}{\phi}\,(P_c - p_o)\,, \tag{4}$$

where p_o is the background pressure in the region. Note the simple equality between the pressures is possible because, unlike previous models, we shall not introduce a surface tension to drive the movement of cells and water, rather cell growth and death are the driving mechanisms.

To this problem we wish to impose boundary conditions that describe how the tumour and any necrotic regions grow. These conditions arise from the following considerations. First, the oxygen concentration is given at some part of the region with $C = c_o$. If there are no external forces acting, the cells are loosely held together, hence the inviscid approximation. It is the cell pressure that presses the cells together and keeps the tumour compact. However, if extracellular water around a cell gets to a pressure higher than the local cell pressure, adjacent cells are ripped from each other and are assumed to rupture. Hence, in our model at all points in the region of cells, it is necessary to have $P_e \leq P_c$. In particular, the boundary must move to ensure this condition continues to be valid at all times. From this and (4) we conclude that at any boundary $P_c = p_o$. However, there is a significant difference between advancing and retreating boundaries. At advancing boundaries the usual kinematic condition holds with the outward normal velocity of the boundary being the normal velocity of the cells, whereas on retreating boundaries we rupture cells to avoid any local region where P_c becomes less than p_o. Hence on such a boundary, the normal pressure gradient (i.e., the cell normal velocity) must be zero.

After appropriate scaling, with

$$C = c_o\,\bar{C}, \qquad \mathbf{x} = \sqrt{\frac{D}{a}}\,\bar{\mathbf{x}}, \qquad P_c = p_o + \frac{D\phi d c_o}{ak(1-\phi)^2}\,\bar{P}, \qquad t = \frac{1-\phi}{dc_o}\,\bar{t},$$

the problem becomes (after dropping the overbar notation)

$$\nabla^2 C = C, \qquad \nabla^2 P = \alpha - C, \qquad \left(\text{where } \alpha = \frac{e}{dc_o}\right).$$

The boundary conditions for the flow problem are

$$-\nabla P \cdot \mathbf{n} \geq 0, \qquad -\nabla P \cdot \mathbf{n} - v_n \geq 0,$$

and

$$(-\nabla P \cdot \mathbf{n})\,(-\nabla P \cdot \mathbf{n} - v_n) = 0$$

with $C = 1$ on some boundary, and where appropriate, no oxygen flux on others. Here $\mathbf{n}$ is the normal vector pointing out of the solution region and v_n is the speed of the boundary in that direction.

Note that although the cell behaviour has been taken as inviscid, the interaction with the extracellular water makes the model for the cell pressure mimic that of a porous media flow, which is the common starting ground for previous models. Our model for P in a tumour is similar to the classical Hele-Shaw problem and to lubrication flows with cavitation (see [8] and references therein). In such problems, the condition on the retreating boundary is commonly called the Reynolds or Swift-Steiber condition. Note that the model has been kept as simple as possible so that there is only one parameter in the problem, namely α which lies in the range $(0 \leq \alpha \leq 1)$, and represents how rapidly the cells die as the oxygen level falls.

AN EXAMPLE OF TUMOUR GROWTH WITH NECROSIS

We consider a problem first studied by Greenspan [9] where a cell culture, modelling a tumour mass, is grown in a test tube resulting in growth that is nominally one-dimensional. We start with a small number of cells in the interval $0 \leq x \leq R(0)$ with $x = 0$ being the stationary impermeable bottom of the tube and $R(t)$ being the upper surface of the tumour with oxygen rich water above. (We have taken the dimensional boundary condition to be $C = c_o$ at this upper surface.) Initially the problem has just the one interface $R(t)$ and satisfies

$$\begin{aligned} &C_{xx} = C, \quad P_{xx} = \alpha - C, && \text{for } 0 \leq x \leq R(t);\\ &C_x = 0 \quad \text{and} \quad P_x = 0, && \text{at } x = 0;\\ &C = 1, \quad P = 0, \quad \text{and} \quad -P_x = R_t, && \text{at } x = R(t). \end{aligned}$$

This problem is solved until $P = 0$ at some point. This occurs first at $x = 0$, and to solve past this point we must introduce another interface $L(t)$ which starts at $L = 0$ and creates the necrotic region $0 \leq x \leq L(t)$. The problem then is

$$\begin{aligned} &C_{xx} = C, \quad P_{xx} = \alpha - C, && \text{for } L(t) \leq x \leq R(t);\\ &C_x = 0, \quad P = 0, \quad \text{and} \quad P_x = 0, && \text{at } x = L(t);\\ &C = 1, \quad P = 0, \quad \text{and} \quad -P_x = R_t, && \text{at } x = R(t). \end{aligned}$$

Note that because all the cells rupture when the retreating interface $L(t)$ passes by, the region $0 \leq x \leq L(t)$ has no cells in it and hence consumes no oxygen.

We can solve these equations to find that, when there is only one interface (before necrosis),

$$\frac{dR}{dt} = \frac{\sinh R}{\cosh R} - \alpha R.$$

This remains valid until a time, denoted by $t = T_c$, when $P = 0$ at $x = 0$ and first occurs when $R(t) = R_c$, where R_c is the positive root of

$$\frac{2}{\cosh R_c} + \alpha R_c^2 - 2 = 0.$$

Subsequently, there are two interfaces which are governed by

$$\frac{dR}{dt} = \frac{\sinh(R-L)}{\cosh(R-L)} - \alpha(R-L) \quad \text{and} \quad \frac{2}{\cosh(R-L)} + \alpha(R-L)^2 - 2 = 0.$$

The behaviour of $R(t)$ is illustrated in Figure 2 generated by numerical solution of the ordinary differential equation for $R(t)$ and the algebraic expression for $L(t)$.

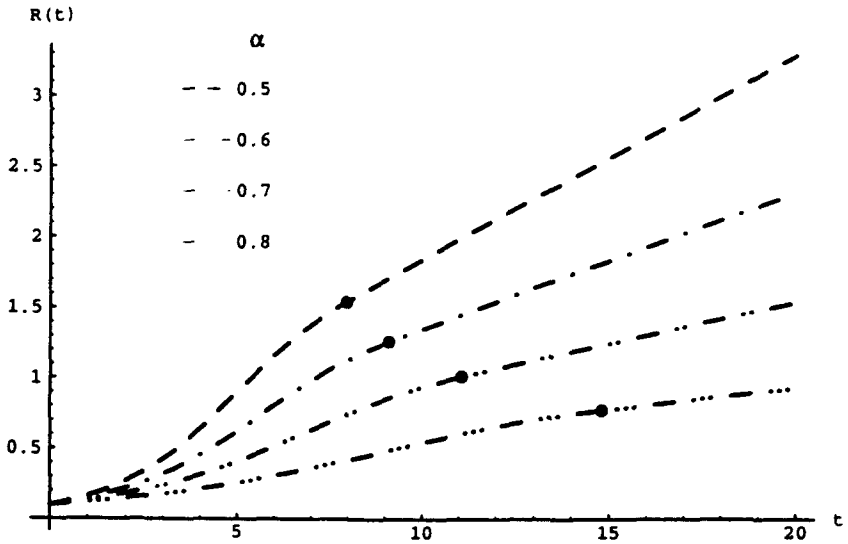

Figure 2. The position of the outer boundary $R(t)$ as the tumour grows, for various values of α. The points • indicate the critical times T_c at which necrosis first occurs.

Hence there is an initial exponential growth in tumour size, but subsequently the region of live cells is of fixed thickness and travels at a constant speed creating a necrotic region growing linearly in time. This behaviour is illustrated in Figure 3 where P, the pressure between cells, is shown across the region at different times. The pressure increases initially as extracellular water is drawn into the region to allow cells to grow. However, once cells start dying near $x = 0$, the pressure drops as water is released from these cells. Finally, the pressure drops to zero and cells start rupturing. In Figure 4 we see the velocity of the cells at various times and see a region of growing cells moving forward while the remaining cells are pushed backwards.

DISCUSSION

We have introduced a model of tumour dynamics that naturally generates necrotic regions as a result of mechanical forces within the tumour. The model differs from previous attempts in that the extracellular water moves through a porous medium while the cells act as an inviscid fluid compacted by reaction to the pressure field generated by the extracellular water. The result is that the cell motion mimics porous media flow. Necrosis occurs when the extracellular water pressure exceeds the cell interaction pressure resulting in rupture of the cells. The mathematical model is similar to that used for cavitation and Hele-Shaw cells. The general behaviour of the model is in line with experimental results. The model is currently being extended to other practical geometries and to situations where the proliferation rate is governed by effects in addition to the oxygen concentration considered here.

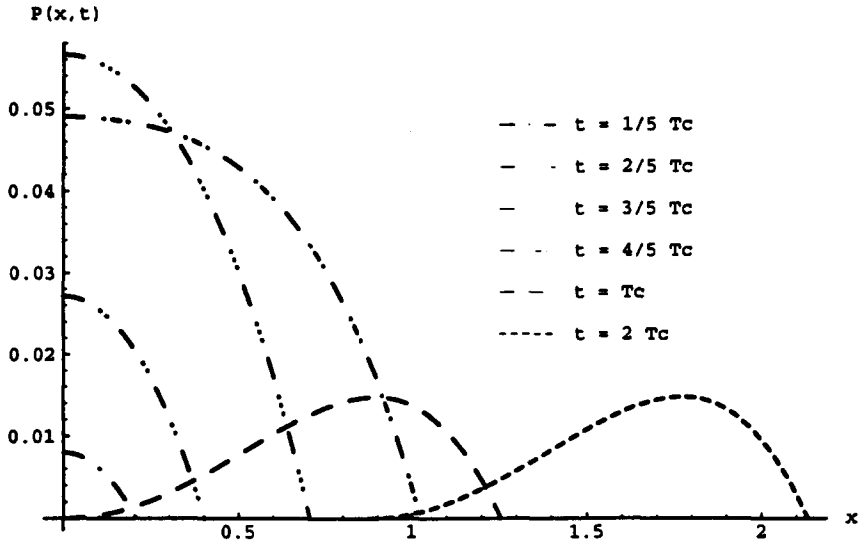

Figure 3. The cell pressure $P(x,t)$ distribution throughout the tumour as it grows, shown for $\alpha = 0.6$ at various multiples of the critical time T_c.

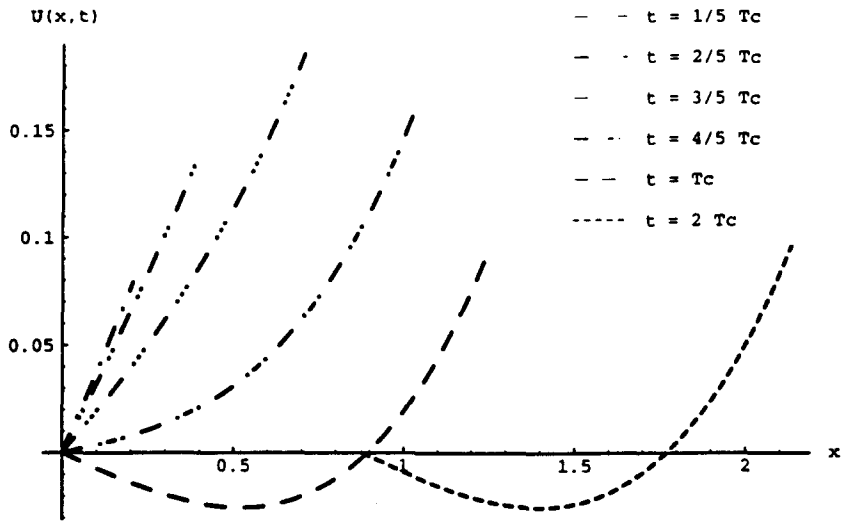

Figure 4. The cell velocity $U(x,t)$ $(= -P_x)$ distribution throughout the tumour as it grows, shown for $\alpha = 0.6$ at various multiples of the critical time T_c.

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